Hot off the Press

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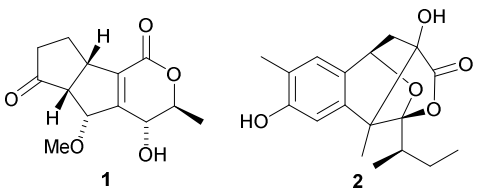
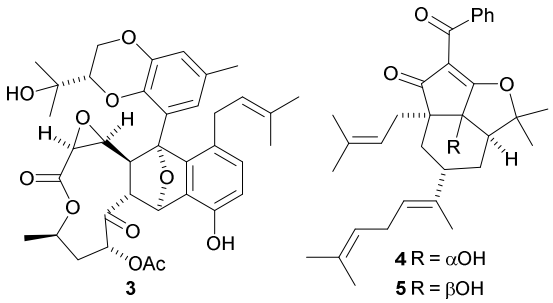
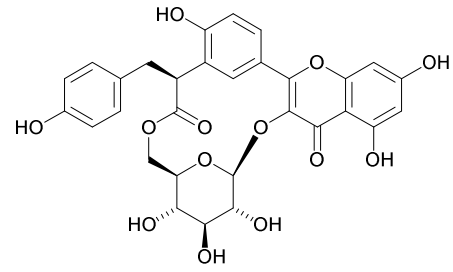
Abstract: A personal selection of 32 recent papers is presented covering various aspects of current developments in bioorganic chemistry and novel natural products such as pepluanol C from *Euphorbia peplus.*

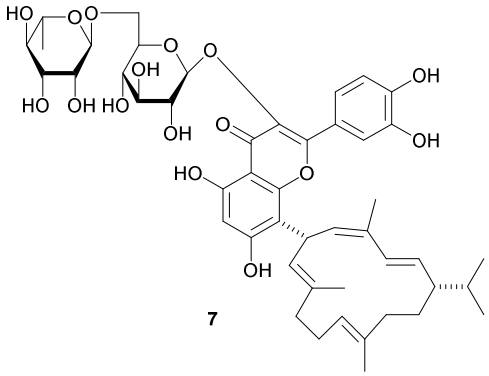
Fusopoltide A **1**, a metabolite of *Fusarium solani*, is the first example of a polyketide with a pentaleno[1,2-*c*]pyran ring system.[1] The structure of fusopoltide A **1** was confirmed by X-ray analysis. A biosynthetic pathway to fusopoltide A **1** from an epimer of jasmonic acid has been proposed. The tetracyclic caged structure of peyronellone A **2**, from *Peyronellaea glomerata*, is thought to be an adduct of an azaphilone and pyruvic acid.[2] Four metabolites, including lithocarpin A **3**, of the deep sea derived *Phomopsis lithocarpus* are proposed to be formed by a [4+2] cycloaddition of an isobenzofuran derived from tenellone B and a macrolide.[3] The acylphloroglucinol derivatives hypermonins A **4** and B **5**, from *Hypericum monogynum*, have a new skeleton.[4] A biosynthetic pathway to the hypermonins has been suggested.





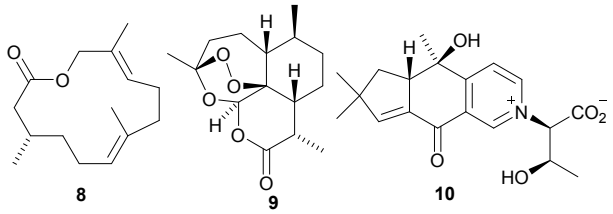
Angustifolinoid A **6**, from flowers of *Elaeagnus angustifolia*, is an unusual macrocyclic flavonoid glucoside.[5] A possible pathway for the cyclisation of the co-occurring tiliroside, that has a 6-*O*-coumaroylglucoside, is discussed by the authors. Nicotabaflavonoidglycoside **7**, from *Nicotiana tabacum*, is the first example of a cembranoid linked to a flavonoid, in this case rutin.[6]



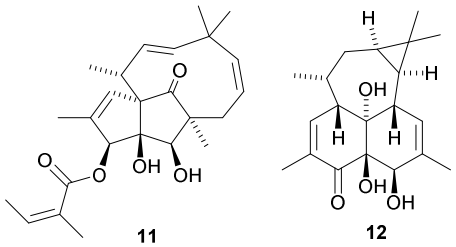


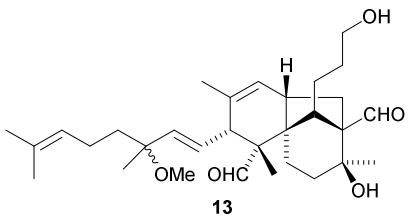
Frogolide **8** has been identified in the scent glands of several African frogs including *Hyperolius viridiflavus*.[7] Frogolide is the first sesquiterpenoid macrolactone to be isolated from frogs as most frog macrolides are derived from the fatty acid pathway. The enantiomer **9** of the natural antimalarial sesquiterpenoid artemisinin has been synthesised and shown to have the same antimalarial activity as the natural isomer.[8] Four antibacterial sesquiterpene-α-amino acid hybrids, such as stereumamide A **10**,

have been isolated from the mushroom *Stereum hirsutum*.[9] The stereumamides are the first examples of sesquiterpenoid-α-amino acid quaternary ammonium salts from natural sources.

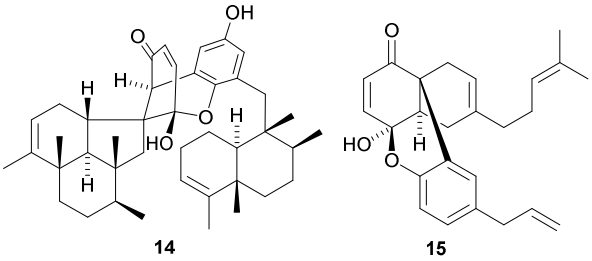


The structures of pepluanols C **11** and D **12**, from *Euphorbia peplus*, were established by X-ray analyses.[10] Pepluanols C **11** and D **12** have new diterpenoid skeletons and biosynthetic pathways have been proposed from an ingenane precursor. Belamchinenin A **13**, from *Belamcanda chinensis*, has a novel triterpenoid skeleton that is proposed to be formed from an iridal precursor.[11]





The dimeric merosesquiterpenoid dysiarenone **14**, from the marine sponge *Dysidea arenaria*, has a novel ring system and it is proposed to be formed from the co-occurring avarone and avarol.[12] Three polycyclic meroterpenoids, such as magterpenoid B **15** have been isolated from the bark of *Magnolia officinalis* var. *biloba*.[13] The racemic magterpenoid B **15** has a novel tetracyclic ring system that is proposed to be formed by a Diels-Alder cycloaddition of the monoterpenoid myrcene with a quinone derivative, followed by hemiacetal formation.



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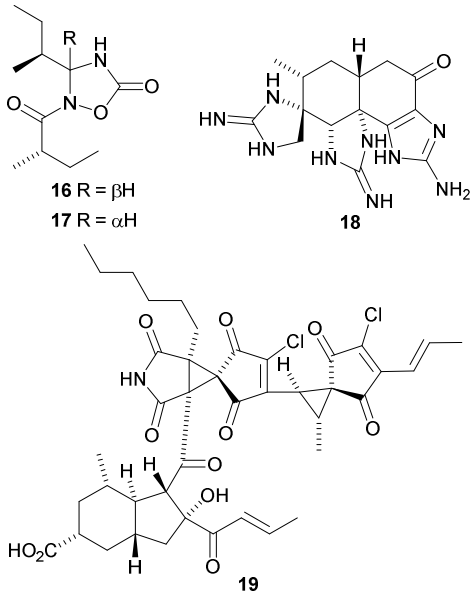
Albatredines A **16** and B **17**, from the edible mushroom *Albatrellus confluens*, feature the first natural occurrence of a 1,2,4-oxadiazolidin-5-one skeleton.[14] Activity-guided isolation of the extract from the zoantharian *Epizoanthus illoricatus* has led to the isolation of KB343 **18** that causes acute convulsions in mice.[15] KB343 **18** is unusual as it has three guanidine groups in one ring system. Cyclohelminthols Y1-Y4 (e.g. Y1 **19**), metabolites of *Helminthosporium velutinum*, have a complex polycyclic ring system including two spirocyclopropanes.[16]



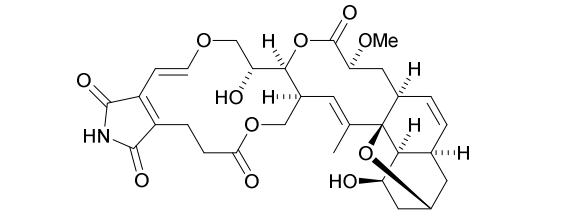
16 R = βH
17 R = αH

18

19

A rare antibacterial macrodilactone streptoseomycin **20**, possessing a pentacyclic 5/14/10/6/6 ring system, has been isolated from marine-derived *Streptomyces seoulensis*.[17] Sequencing of the ~76 kb biosynthetic gene cluster has led to a proposed biosynthetic pathway involving coupling of a tricyclic nonaketide and an α-ketoglutarate-derived dialkylmaleimide. An iodoanthracene **21**, containing a fused

thiolactone, has been identified as a mid-pathway intermediate during the biosynthesis of the enediyne polyketide dynemicin A **22**.[18] Further evidence for this unusual iodinated intermediate was provided by the selective incorporation of **21** into the final product. This discovery is a key advance in unravelling the complex biosynthetic pathway of dynemicin A.



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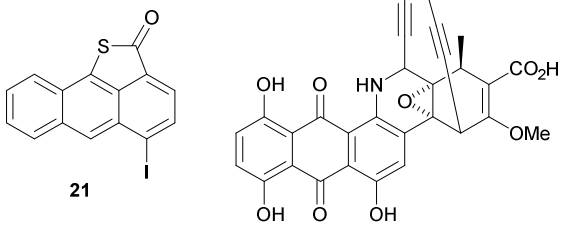
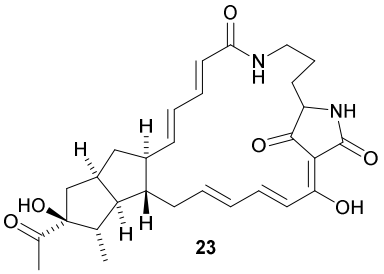


21 **22**

Activation of a polycyclic tetramate macrolactam gene cluster in *Streptomyces* sp. S10 by promoter engineering, followed by heterologous expression, has generated four new products, including combamide A **23**.[19] Using combinatorial biosynthesis that involved variation of redox enzymes, two further analogues were also generated. In vitro reconstitution of the enzymes in the *amb* gene cluster has revealed the biosynthetic pathway of the non-proteinogenic amino acid, methoxyvinylglycine **24**.[20] The amino acid is generated from glutamic acid using two non-ribosomal peptide synthetases (NRPSs) and two iron-dependent α-ketoglutarate oxygenases. Evidence was also provided for a hydroxylated intermediate that introduces unsaturation via a 2,3-dehydration mechanism.



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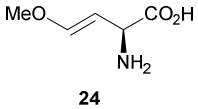

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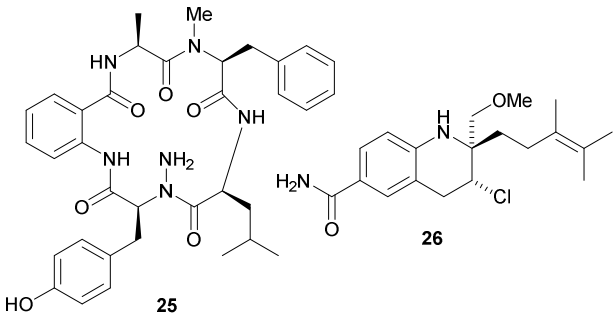
Genome sequencing, bioinformatics and heterologous expression have been used to investigate the biosynthesis of the cycloaspeptides, such as cycloaspeptide A **25**, bioactive pentapeptides from filamentous fungi.[21] The cycloaspeptide gene cluster was shown to contain a minimal 5-module NRPS and a novel *trans*-acting *N*-methyltransferase. Benzastatins, a family of bacterial natural products that include indoline and tetrahydroquinoline scaffolds (e.g. benzastatin C **26**) are proposed to be derived by cyclisation of geranylated *p*-aminobenzoic acids. Analysis of the benzastatin gene cluster from *Streptomyces* sp. RI18 has revealed a cytochrome P450 enzyme, BezE, that catalyses this cyclisation via an iron nitrenoid and an aziridine intermediate.[22]



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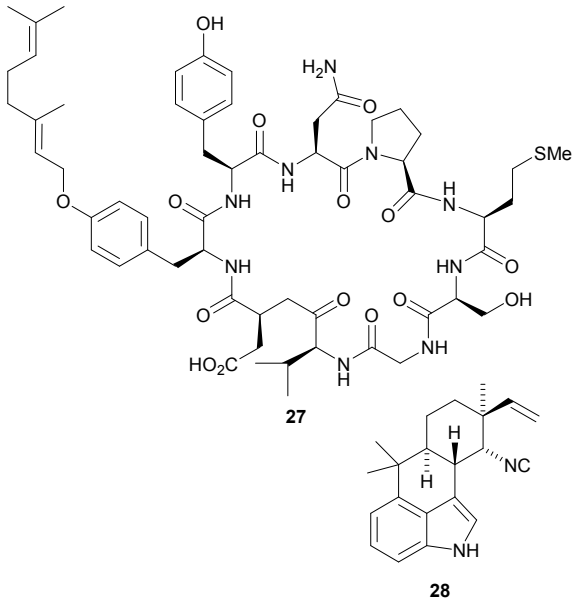
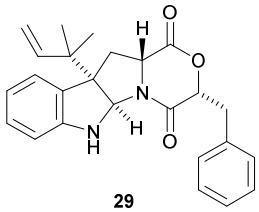
26

A geranyltransferase enzyme, PirF from the piricyclamide pathway has been shown to perform post-translational and regioselective geranylation of tyrosine in cyanobactin biosynthesis.[23] Investigation of the enzyme allowed both structural characterisation of the product, piricyclamide 7005E1 **27** and an understanding of substrate specificity, suggesting synthetic biology applications. The crystal structure of HpiC1, a Stig cyclase from *Stigonematales*, an enzyme responsible for three mechanistic steps, a

Cope rearrangement, a 6-*exo*-*trig* cyclisation and an electrophilic aromatic substitution during the biosynthesis of 12-*epi*-hapalindole U **28** has been solved.[24] A combination of mutational analysis that has identified the enzyme active site and, DFT calculations have generated detailed insight of the enzymatic processes that control the stereochemical outcome and product formation.



Fungal artificial chromosomes and metabolic scoring (FAC-MS) technology has been used to identify the biosynthetic gene cluster responsible for the formation of acu-dioxomorpholine A **29**, a secondary metabolite from the fungus, *Aspergillus aculeatus*.[25] This allowed characterisation of a NRPS with a novel condensation domain that is proposed to utilise an arginine active site for ester bond formation. The use of phylogenetic analysis of cytochrome P450 enzymes from the CYP71 family involved in sesquiterpenoid metabolism has identified the sunflower enzyme capable of producing the sesquiterpene lactone, eupatolide.[26] The *Helianthus annuus* eupatolide synthase (HaES) was shown to form eupatolide **30** by a 6,7-*trans* lactonisation of 8β-hydroxygermacrene A acid (Scheme 1).



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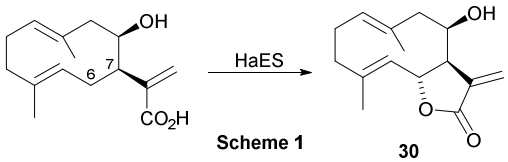

Scheme 1

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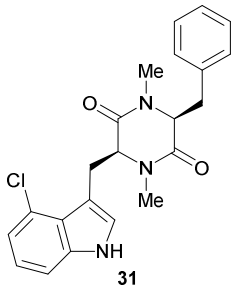
A new approach for the biosynthesis of unnatural variants of thaxtomin phytotoxins, potential herbicides from *Streptomyces scabies*, has been developed.[27] Feeding indole derivatives to an engineered *S. albus* strain containing the thaxtomin NRPS and a tryptophan synthase resulted in the production of a series of novel thaxtomins (e.g. **31**). A rhodium(I)-catalysed addition and condensation reaction of alkyl vinyl ketones and 2-aminophenyl boronic acids, followed by a cyclohexylamine oxidase (CHAO) deracemization has allowed the preparation of a range of alkaloidal tetrahydroquinolines (Scheme 2).[28] The deracemization could be performed on a preparative scale, producing the targets in up to >99% ee.



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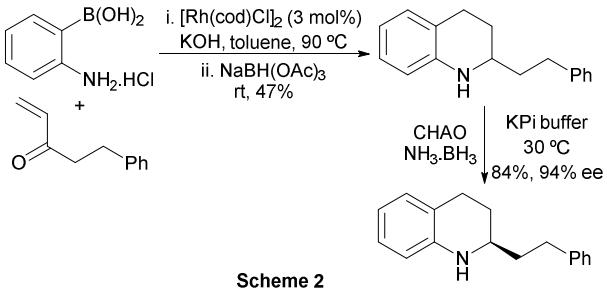
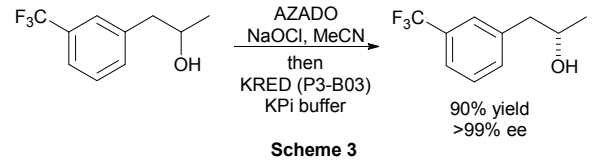
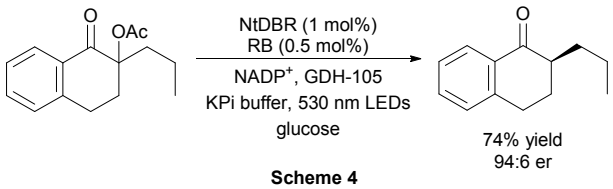


Scheme 2

A one-pot organocatalytic oxidation and a biocatalytic reduction has been developed for the deracemisation of secondary alcohols.[29] Oxidation of the racemic alcohols using sodium hypochlorite and 2-azaadamantane *N*-oxyl (AZADO), followed by asymmetric reduction with a ketoreductase, generated the secondary alcohols in high yields and excellent ee (Scheme 3). Using visible-light irradiation, xanthene-based photocatalysts have enabled a double-bond reductase catalysed asymmetric deacetoxylation of α-acetoxytetralones.[30] Use of Rose Bengal (RB) as a photocatalyst and the double-bond reductase from *Nicotiana tabacum* (NtDBR), allowed the asymmetric synthesis of a range of tetralones in high to excellent enantiomeric ratios (Scheme 4).



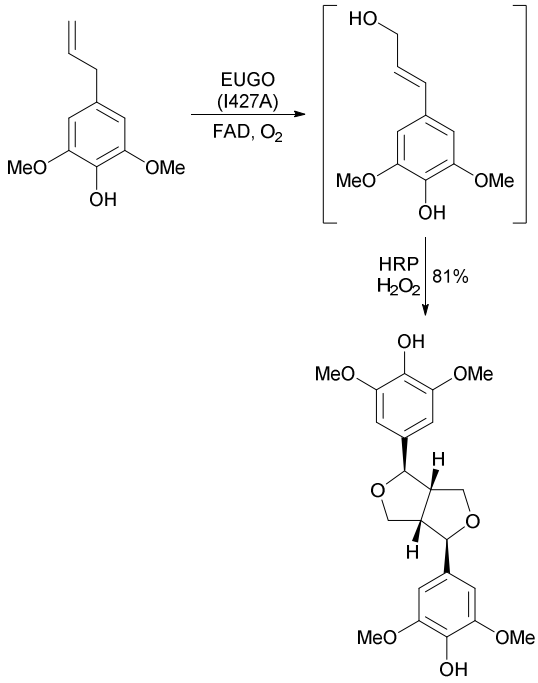
Scheme 3



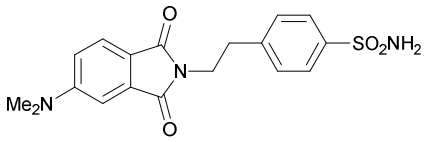
Scheme 4

A one-pot, fully coupled two-step biocatalytic process has been developed for the synthesis of (±)-syringaresinol, a lignan with a range of medicinally important properties.[31] Engineered eugenol oxidase (EUGO) was initially used to convert 2,6-dimethoxy-4-allylphenol to the corresponding sinapyl alcohol (Scheme 5). Horseradish peroxidase (HRP) mediated coupling then produced syringaresinol as the major product in 81% yield. A small-molecule probe **32** has been developed to track *holo*-carbonic anhydrase in cell lysates and live-cells models of zinc dyshomeostasis.[32] The probe which contains a sulfonamide moiety for the high

affinity binding of the carbonic anhydrase active site zinc ion, displays a 12-fold increase in fluorescence upon binding to the enzyme.



Scheme 5



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References

1 K. Chen, W. Sun, Q. Bie, X. Liu, C. Chen, J. Liu, Y. Xue, J. Wang, Z. Luo, H. Zhu and Y. Zhang, *Tetrahedron Lett*., 2018, **59**, 2679.

2 T.-X. Li, R.-H. Liu, X.-B. Wang, J. Luo, J.-G. Luo, L.-Y. Kong and M.-H. Yang, *J. Nat. Prod*., 2018, **81**, 1148.

3 J. Xu, H. Tan, Y. Chen, S. Li, Z. Huang, H. Guo, H. Li, X. Gao, H. Liu and W. Zhang, *Org. Chem. Front*., 2018, **5**, 1792.

4 Y.-R. Zeng, P. Yi, W. Gu, C.-X. Xiao, L.-J. Huang, D.-S. Tian, H. Yan, D.-Z. Chen, C.-M. Yuan and X.-J. Hao, *Org. Biomol. Chem*., 2018, **16**, 4195.

5 X. Chen, Y. Liu, G. Chen, C. Gong, S. Li, H. Hua and T. Yuan, *Tetrahedron Lett*., 2018, **59**, 2610.

6 C.-Y. Yang, Y. Lin, H.-X. Yuan, W.-P. Yang, X. Wei and Z.-L. Huang, *Fitoterapia*, 2018, **128**, 242.

7 M. Menke, K. Melnik, P. S. Peram, I. Starnberger, W. Hödl, M. Vences and S. Schulz, *Eur. J. Org. Chem.*, 2018, 2651.

8 J. Krieger, T. Smeilus, M. Kaiser, E.-J. Seo, T. Efferth and A. Giannis, *Angew. Chem. Int. Ed.*, 2018, **57**, 8293.

9 Y.-C. Duan, J. Feng, N. Bai, G.-H. Li, K.-Q. Zhang and P.-J. Zhao, *Fitoterapia*, 2018, **128**, 213.

10 L.-S. Wan, Y. Nian, X.-R. Peng, L.-D. Shao, X.-N. Li, J. Yang, M. Zhou and M.-H. Qiu, *Org. Lett*., 2018, **20**, 3074.

11 G. Ni, J.-Y. Li and D.-Q. Yu, *Org. Biomol. Chem*., 2018, **16**, 3754.

12 W.-H. Jiao, B.-H. Cheng, G.-D. Chen, G.-H. Shi, J. Li, T.-Y. Hu and H.-W. Lin, *Org. Lett*., 2018, **20**, 3092.

13 C. Li, C.-J. Li, J. Ma, F.-Y. Chen, L. Li, X.-L. Wang, F. Ye and D.-M. Zhang, *Org. Lett*., 2018, **20**, 3682.

14 S. Zhang, Y. Huang, S. He, H. Chen, Z. Li, B. Wu, J. Zuo, T. Feng and J. Liu, *RSC Adv*., 2018, **8**, 23914.

15 K. Matsumura, T. Taniguchi, J. D. Reimer, S. Noguchi, M. J. Fujita and R. Sakai, *Org. Lett*., 2018, **20**, 3039.

16 S. Tanaka, K. Tanaka, H. Maeda and M. Hashimoto, *J. Org. Chem*., 2018, **83**, 5688.

17 B. Zhang, K. B. Wang, W. Wang, S. F. Bi, Y. N. Mei, X. Z. Deng, R. H. Jiao, R. X. Tan and H. M. Ge, *Org. Lett*., 2018, **20**, 2967.

18 D. R. Cohen and C. A. Townsend, *Angew. Chem. Int. Ed*., 2018, **57**, 5650.

19 Y. Liu, H. Wang, R. Song, J. Chen, T. Li, Y. Li, L. Du and Y. Shen, *Org. Lett*., 2018, **20**, 3504.

20 J. B. Patteson, Z. D. Dunn and B. Li, *Angew. Chem. Int. Ed*., 2018, **57**, 6780.

21 K. M. J. de Mattos-Shipley, C. Greco, D. M. Heard, G. Hough, N. P. Mulholland, J. L. Vincent, J. Micklefield, T. J. Simpson, C. L. Willis, R. J. Cox and A. M. Bailey, *Chem. Sci*., 2018, **9**, 4109.

22 H. Tsutsumi, Y. Katsuyama, M. Izumikawa, M. Takagi, M. Fujie, N. Satoh, K. Shin-ya and Y. Ohnishi, *J. Am. Chem. Soc*., 2018, **140**, 6631.

23 M. Morita, Y. Hao, J. K. Jokela, D. Sardar, Z. Lin, K. Sivonen, S. K. Nair and E. W. Schmidt, *J. Am. Chem. Soc*., 2018, **140**, 6044.

24 S. A. Newmister, S. Li, M. Garcia-Borràs, J. N. Sanders, S. Yang, A. N. Lowell, F. Yu, J. L. Smith, R. M. Williams, K. N. Houk and D. H. Sherman, *Nat. Chem. Biol*., 2018, **14**, 345.

25 M. T. Robey, R. Ye, J. W. Bok, K. D. Clevenger, M. N. Islam, C. Chen, R. Gupta, M. Swyers, E. Wu, P. Gao, P. M. Thomas, C. C. Wu, N. P. Keller and N. L. Kelleher, *ACS Chem. Biol*., 2018, **13**, 1142.

26 M. Frey, K. Schmauder, I. Pateraki and O. Spring, *ACS Chem. Biol*., 2018, **13**, 1536.

27 M. Winn, D. Francis and J. Micklefield, *Angew. Chem. Int. Ed*., 2018, **57**, 6830.

28 S. C. Cosgrove, S. Hussain, N. J. Turner and S. P. Marsden, *ACS Catal*., 2018, **8**, 5570.

29 E. Liardo, N. Ríos-Lombardía, F. Morís, J. González-Sabín and F. Rebolledo, *Eur. J. Org. Chem*., 2018, 3031.

30 K. F. Biegasiewicz, S. J. Cooper, M. A. Emmanuel, D. C. Miller and T. K. Hyster, *Nat. Chem*., 2018, **10**, 770.

31 M. Habib, M. Trajkovic and M. W. Fraaije, *ACS Catal*., 2018, **8**, 5549.

32 R. Mehta, M. H. Qureshi, M. K. Purchal, S. M. Greer, S. Gong, C. Ngo and E. L. Que, *Chem. Commun*., 2018, **54**, 5442.